A Modern Approach for Evaluating Human Cancer Risk from Exposure to Chemicals

Douglas C. Wolf, D.V.M., Ph.D., FIATP, ATS
Senior Fellow
Product Safety
Syngenta Crop Protection, LLC
doug.wolf@syngenta.com

Overview

Using knowledge accumulated from intended use and class of chemistry will focus the questions that need to be answered to protect human populations from chemical cancer risk.

“To innovate is not to reform”
Edmund Burke (1729–1797), Irish philosopher, statesman.

Topics

Context

Unified Theory of Carcinogenicity

Protecting Public Health

Cumulative risk

Path forward

What problem is being addressed?

Approach from the 1970's (*how we still think about cancer risk for chemicals*):

Identify the hazards a chemical could cause and prevent them by eliminating the chemical's use.









How we should be thinking today.

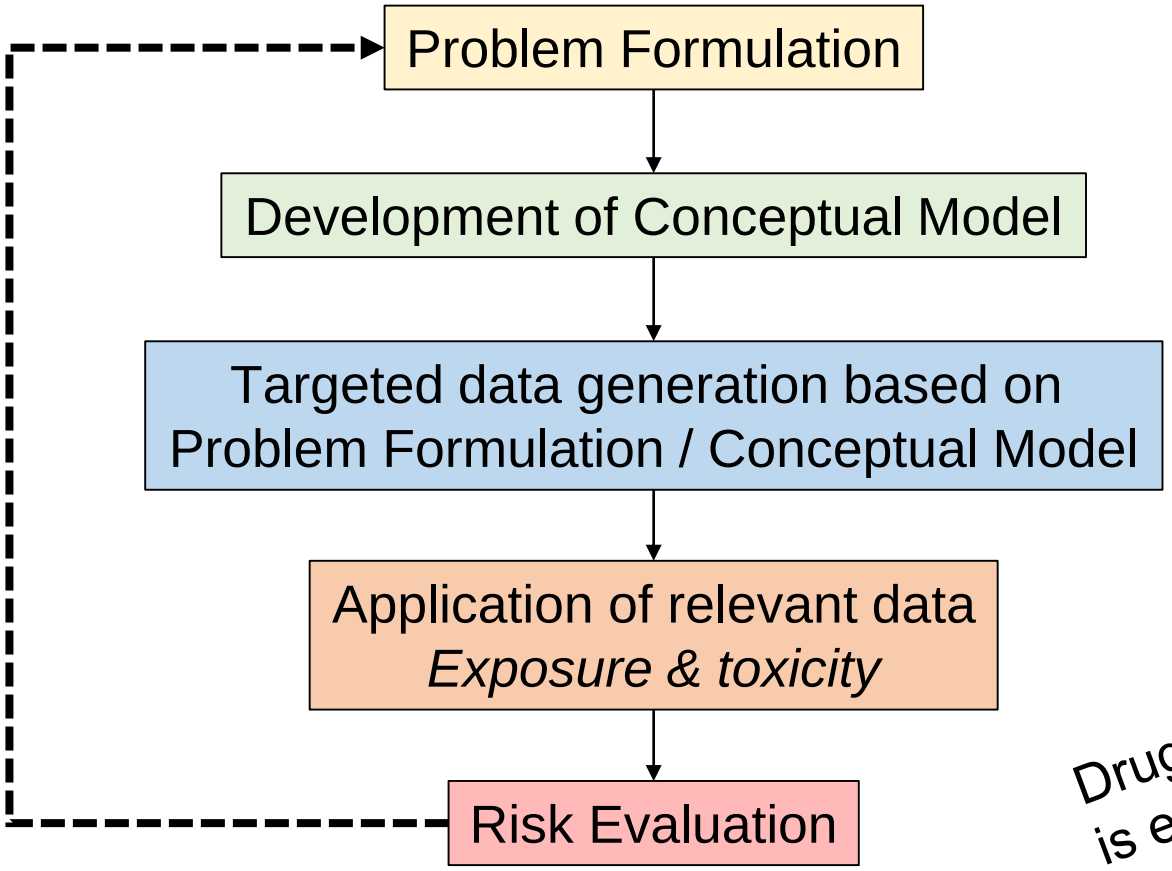
Identify and characterize the **context** in which a xenobiotic could result in an adverse effect so that appropriate **risk management** measures can be taken to protect human health.

We can't solve problems by
using the same kind of thinking
we used when we created them.

Adaptation of an Einstein Quote.

Cosmetics testing is animal free

New Paradigm



Drug development is exposure-based

Carcinogenesis

Cancer is due to mistakes in the DNA.

More than one mistake in DNA is necessary.

The mistakes need to accumulate in a single cell (clonal origin of cancer).

The cell population at risk are the tissue pluripotent (stem) cells.

Every time DNA replicates, permanent mistakes could occur.

Carcinogenesis is a stochastic process.

Doe et al., Reg Tox Pharm 103:124-129, 2019

Hallmarks of Cancer

"While many researchers have found the Hallmarks of Cancer concept to be highly useful in attempting to conceptualize the cell-biological properties of individual cancer cells and the distinct cellular phenotypes that contribute to cancer cell behavior, I fear that **the HoC do not really enlighten most discussions on human carcinogens and chemical exposure risk**, which are generally governed by complex organismic and tissue effects that are not in any way addressed by the HoC. (The only exception to this are frankly mutagenic agents for which the associated risk evaluations are, by comparison, relatively straightforward.)"
personal communication, Bob Weinberg

"**I cannot think of anything further removed from the Hallmarks as measurements of chemical exposure and carcinogens.** The Hallmarks are products of carcinogenic processes, where such carcinogenic processes have acted in a "hit-and-run" fashion, done their work and then disappeared off stage. **I don't see why people can think otherwise**."
personal communication, Bob Weinberg

"**a chemical increasing cancer risk must either have a mutagenic (direct) effect or an indirect effect by increasing the proliferation rate**."
personal communication, Cristian Tomasetti

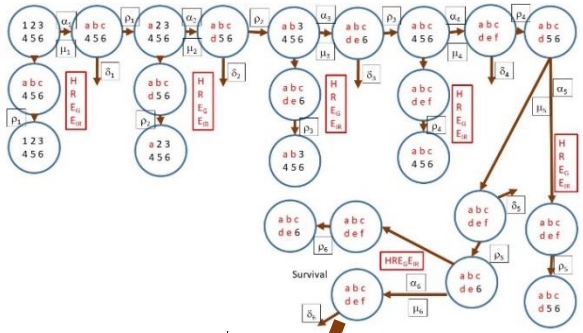
Hanahan D and Weinberg RA. (2000) Cell 100:57-70.
Hanahan D and Weinberg RA. (2011) Cell 144:646-674.
Tomasetti C, Lu L and Vogelstein B (2017) Science 355, 1330–1334
Tomasetti C and Vogelstein B (2015) Science 347, 78-81

Population model of chemical carcinogenesis.
Requires sufficient exposure and maintaining a sustained stress environment.

Source
- **Fate/Transport**
  - **Exposure**
    - **Tissue Dose**
      - **Biologic Interaction**
        - **Perturbation through Toxicity Pathway**
        - **Adaptive Stress Responses**

Sufficient **continual exposure** and a **sustained stress** environment, cells adapt, accumulate survival mutations and function within the ongoing stress.

H Hereditary Factor
R Constitutive Replication
E_G Genotoxic Environmental Factor
E_{IR} Environmentally Induced Replication



α – Proliferation
μ – Mutation
δ – Death
ρ – Repair

Adapted Cell to maintain normal biological function

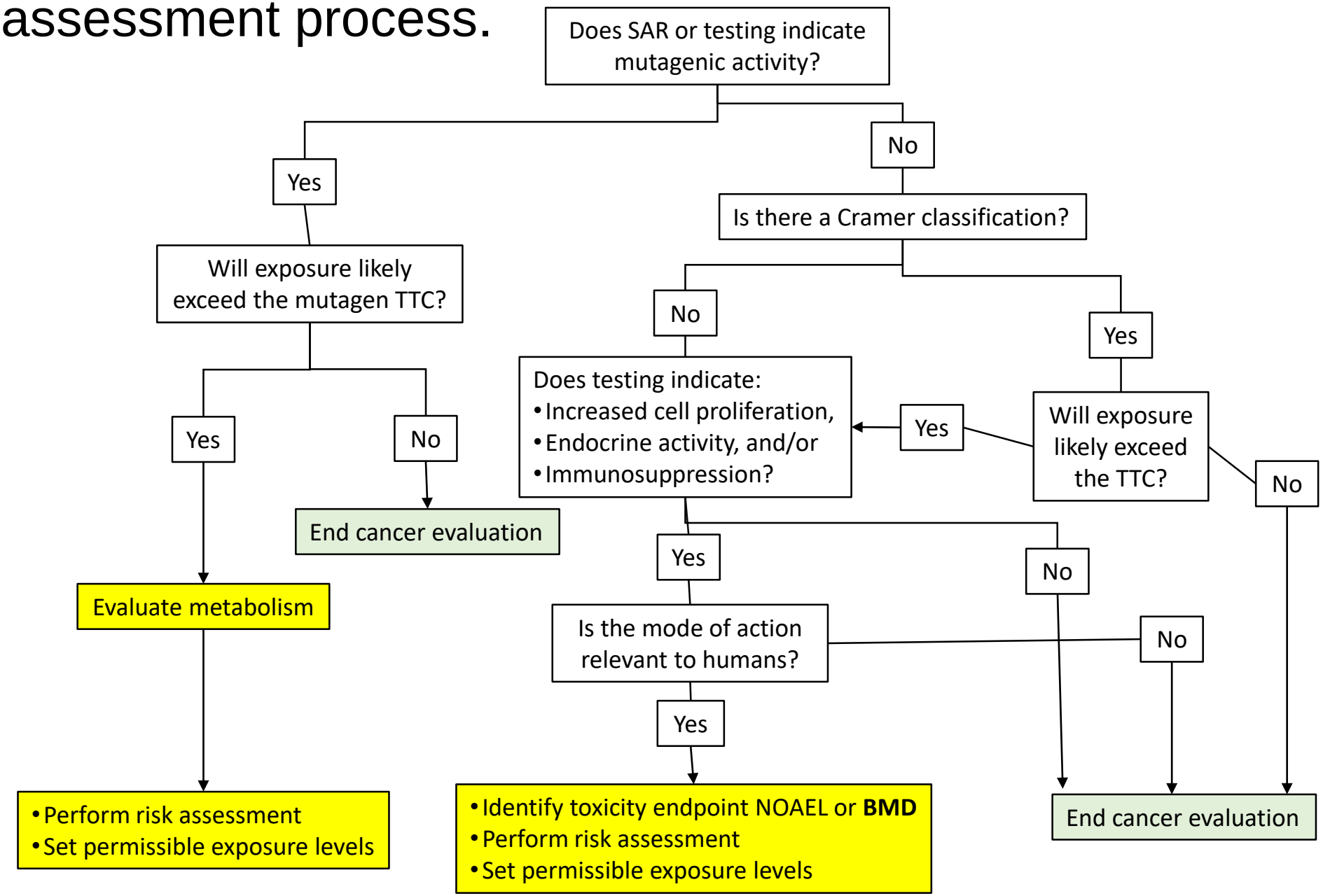
Malignancy

R
E_{IR}

Wolf et al., Reg Toxicol Pharmacol 103:86-92, 2019

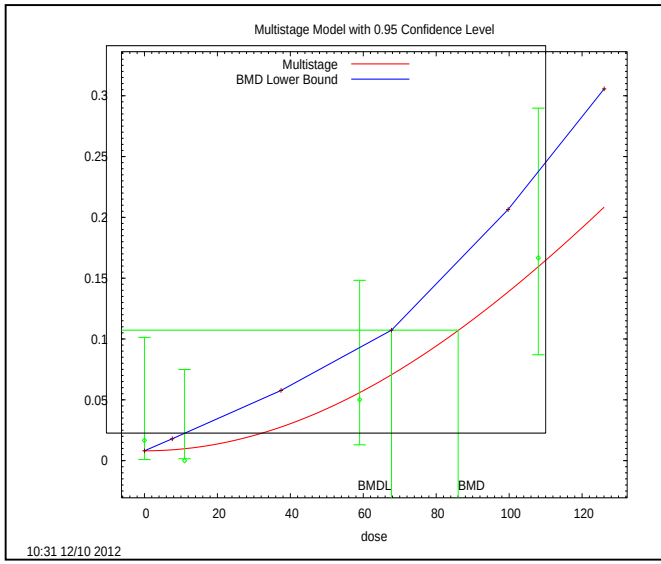
Suggested carcinogenicity assessment process.

Cohen, Current Opin Toxicol 3:6-11, 2017;
Cohen et al., Reg Tox Pharm 103:100-105, 2019



Benchmark Dose-Response Modeling: 21st Century Application in Safety Assessment

Bhat et al., Toxicol Sci 136:205-215, 2013
Geter et al., Toxicol Sci 138:425-445, 2014
Lake et al., Toxicol Sci 149:312-325, 2016



Human health is protected by limiting exposures to below the selected BMD_T.

	Cyproconazole	Epoxiconazole	Propiconazole	Triademifon	Myclobutanil
Adenoma	3.0	>72	68	270	Not observed
Carcinoma	>28	33	>108	Not observed	
Adenoma or Carcinoma	**2.1**	**33**	**65**	**270**	
30 d median transcriptional $BMDL_T$	**9**	**16**	**51**	**58**	**78**

Same potency gradient and very consistent in potency
Bhat et al., Toxicol Sci 136:205-215, 2013

Cumulative Cancer Risk Evaluation Conceptual Framework

www.risk21.org

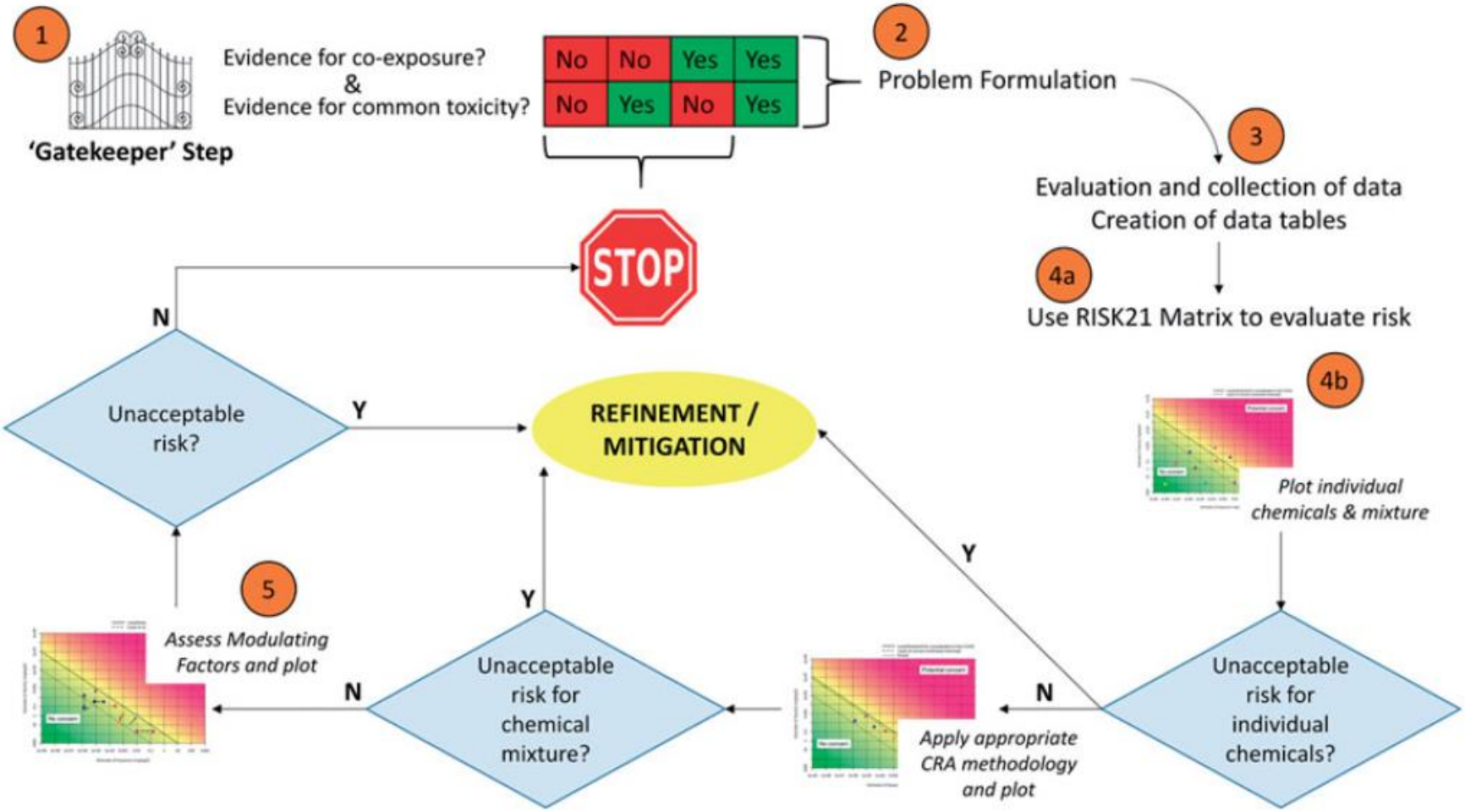


Figure 1. General conceptual framework of the proposed RISK21 approach to CRA.

Moretto et al., Crit Rev Toxicol; 47: 85-97, 2016

Solomon et al., Crit Rev Toxicol; 46:835-844, 2016

Summary

In vitro and shorter-term *in vivo* assays can be used to evaluate carcinogenic potential.

Identify primary effects that lead to DNA changes, damage, or increases in cell division.

Protect health by setting exposure limits that prevent primary effects.

Protects against all adverse long term effects, including cancer.

Modes of action leading to induction of tumors are identified through determination of hazardous properties such as Mutagenicity, Genotoxicity and Target Organ Toxicity.

A separate category for Carcinogenicity provides no additional public health protection.

Avoid waste of money, time, and animals and equally health protective to prevent adverse outcomes from chronic exposure which includes cancer.

These tools can also be incorporated into the evaluation for cumulative risk from combined exposure.

Conclusions

This approach will allow human health to be safeguarded and far more chemicals to be sufficiently evaluated while eliminating a costly, outmoded, and unnecessary assay.

The long-term rodent bioassay is not required to evaluate the potential for carcinogenicity in humans and protect public health.

"The difficulty lies, not in the new ideas, but in escaping from the old ones"
John Maynard Keynes (1883–1946), British economist